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Canadian Adverse Reaction Newsletter

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Scope

This quarterly publication alerts health professionals to potential signals detected through the review of case reports submitted to Health Canada. It is a useful mechanism to disseminate information on suspected adverse reactions to health products occurring in humans before comprehensive risk–benefit evaluations and regulatory decisions are undertaken. The continuous evaluation of health product safety profiles depends on the quality of your reports.

Reporting Adverse Reactions

Contact Health Canada or a Regional AR Centre free of charge
Phone: 866 234-2345
Fax: 866 678-6789

Form available at:
www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/index_e.html

Intrathecal baclofen (Lioresal): suspected adverse incidents associated with implantable drug pump system

Baclofen (Lioresal) is a muscle relaxant and antispastic agent.[1] Intrathecal baclofen (ITB) is indicated for the management of severe spasticity in patients with spinal cord injury or multiple sclerosis unresponsive to oral baclofen therapy or who experience unacceptable adverse reactions at effective oral doses. It is also used in patients with spasticity of cerebral origin.[1] ITB injection, which delivers the drug directly to its site of action, can achieve cerebrospinal fluid levels up to 30 times higher than those achieved using oral baclofen therapy, with minimal serum concentrations.[2] Patients receive baclofen as a continuous intrathecal infusion from a surgically implanted pump system.[1] During chronic therapy, most patients require gradual dose increases because of decreased responsiveness or disease progression.

From Jan. 1, 1992, to June 30, 2005, Health Canada received 21 reports of adverse reactions suspected of being associated with ITB. Ten reports implicated the implantable drug pump system (IDPS). Of these 10 reports, 5 involved problems specific to the catheter system and 5 involved coma following implantation surgery (suspected improper pump preparation leading to inadvertent bolus). Device-related adverse events are mentioned in the Lioresal Intrathecal product monograph[1] and in the Medtronic pump systems information.[3]

One of these reports has already been published in the medical literature and describes a case with confusing symptomatology.[4] A 6-year-old boy with cerebral palsy underwent implantation of an intrathecal baclofen pump to manage his spasticity. Two years later, he was admitted to hospital twice in a 3-day span with symptoms of apparent baclofen overdose. His parents described a 2-month history consistent with intermittent symptoms of baclofen overdose in the morning (reduced consciousness, hypotonia) followed by symptoms of baclofen tolerance or withdrawal later in the day (increased rigidity). Routine investigation of the IDPS did not yield any significant findings, but a microfracture of the catheter was visible on electron microscopy. The catheter was replaced, the patient recovered, and a lower maintenance dose was established. In this case, the intermittent symptomatology was thought to have been due to posture-

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related effects on the catheter microfracture. It was postulated that the microfracture was closed when the patient was supine at night and forced open when he was positioned upright during the day, leading to leakage of the medication.[4]

The exact nature of catheter-related complications associated with the use of IDPS may not always be identified using the various procedural checks in an established protocol.[5] In some cases, surgery fails to identify the cause of the catheter malfunction; however, replacement of the catheter may restore the clinical response to ITB.[5]

Health care professionals should be aware of potential IDPS-related adverse events, which may present with confusing signs and symptoms. Device-related issues should be considered when evaluating the need for dose adjustments.

Andrew Gaffen, BSc, DDS; Momir Nesic, MD, PhD; Gina Coleman, MD, Health Canada

References

1. *Lioresal Intrathecal (baclofen injection)* [product monograph]. Dorval (QC): Novartis Pharmaceuticals Canada Inc.; 2002.
2. Anderson KJ, Farmer JP, Brown K. Reversible coma in children after improper baclofen pump insertion. *Paediatr Anaesth* 2002;12(5):454-60.
3. Medtronic pain therapies. Intrathecal drug delivery: important safety information and risks. Minneapolis: Medtronic Inc.; 2001. Available: www.medtronic.com/neuro/paintherapies/pain_treatment_ladder/drug_infusion/risks/drug_risk.html (accessed 2005 July 18).
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5. Bardutzky J, Tronnier V, Schwab S, Meinck HM. Intrathecal baclofen for stiff-person syndrome: life-threatening intermittent catheter leakage. *Neurology* 2003;60(12):1976-8.

Statins and memory loss

The role of HMG–CoA reductase inhibitors, or statins, in cardiovascular protection is well established. However, evidence in the current literature is conflicting as to the effect of statins on cognitive function.[1] It has been postulated that statins may prevent dementia of the Alzheimer's type through inhibition of β-amyloid formation and thus decreased production of neurofibrillary tangles and plaques.[2] Other studies have suggested that statins can contribute to memory loss.[1-4] The proposed mechanism relates to cholesterol's essential role in myelin production. Statins, especially the more lipophilic ones (e.g., atorvastatin and simvastatin), may cross the blood–brain barrier and decrease the amount of central nervous system (CNS) cholesterol necessary for the formation of myelin.[2,3] Inadequate myelin production may result in demyelination of nerve fibres in the CNS and thus lead to memory loss.[2] Memory impairment is listed in the product monograph for Pravachol.[5]

From the date of marketing of statins in Canada to May 31, 2005, Health Canada received 19 reports of amnesia suspected of being associated with these drugs (Table 1). The onset was reported to occur within 1 month after starting statin therapy in 5 cases, within 1 year in 7 cases and after 1 year in 3 cases. Four cases did not report an onset date. Eleven reports described that the amnesia resolved or improved when the drug was discontinued or the dose reduced, and one of them also described a positive rechallenge. Other reports did not provide this information.

Given these findings, changes in cognitive status temporally associated with statin therapy should be monitored.[2]

Michel Trottier, BScPhm, RPEBC, RPh, Health Canada

References

1. Wagstaff LR, Mitton MW, Arvik BM, Doraiswamy PM. Statin-associated memory loss: analysis of 60 case reports and review of the literature. *Pharmacotherapy* 2003;23(7):871-80.
2. King DS, Wilburn AJ, Wofford MR, Harrell TK, Lindley BJ, Jones DW. Cognitive impairment associated with atorvastatin and simvastatin. *Pharmacotherapy* 2003;23(12):1663-7.
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Table 1: Reports submitted to Health Canada of amnesia* suspected of being associated with statins from date marketed in Canada to May 31, 2005†

Variable	Atorvastatin	Cerivastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
Date marketed	1997	1998‡	1994	1988	1990	2003	1990
Total no. of AR reports with amnesia	8	1	0	2	0	4	4
Positive dechallenge§	4	1	–	2	–	2	1
Median age (and range) of patients, yr	70 (50–78)¶	NR	–	61 (41–81)	–	57 (51–69)	67 (65–81)¶

Note: AR = adverse reaction, NR = not reported.

*Includes forgetfulness, memory disturbance, memory impairment and memory loss according to the *World Health Organization Adverse Reaction Terminology* (WHOART).

†**These data cannot be used to determine the incidence of ARs or to make quantitative drug safety comparisons between the products because ARs are underreported and neither patient exposure nor the amount of time the drug was on the market has been taken into consideration.**

‡Cerivastatin withdrawn from the market in 2001.

§Response to withdrawal of the drug.

¶Age unknown in 1 case.

Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Pms-Chloral Hydrate and pms-Potassium Chloride: medication incident

In 2004, Health Canada received a report of an adverse reaction involving a medication incident related to look-alike product labelling and packaging. An 80-year-old man was prescribed potassium chloride. When the prescription was refilled, pms-Chloral Hydrate 100 mg/mL syrup was dispensed in place of pms-Potassium Chloride 20 mmol/15 mL oral solution. The stock bottles of these products, similar both in packaging and labelling (Fig. 1, left), were stored side-by-side on the pharmacy shelf. The patient received a total of 300 mL (30 g) of chloral hydrate over approximately 40 hours and died shortly thereafter. Postmortem screening indicated highly toxic blood levels of trichloroethanol, the major active metabolite of chloral hydrate.[1,2] The patient was taking multiple concomitant medications, but there was no suggestion of any interactions with the chloral hydrate.

The Institute for Safe Medication Practices Canada (ISMP Canada) has indicated that it also received a report of the event and will be issuing an information bulletin with detailed preventive strategies. Since the occurrence of the fatal incident, Pharmascience, the manufacturer of both products, has modified the labels to improve their differentiation (Fig. 1, right).

Look-alike packaging and labelling of health products can increase the risk of errors when dispensing or administering medications. Such errors can result in serious patient harm, and sometimes in death.[3,4] The processes and designs of medication systems should be examined to help prevent human error. Creating safe medication systems requires a culture that supports identifying errors and leadership.[5] Information on where and how errors occur can be acquired through voluntary medication incident reporting systems.

Health Canada, ISMP Canada and the Canadian Institute for Health Information are currently developing the Canadian Medication Incident Reporting and Prevention System, a program that will strengthen the Canadian health care system's capacity to report, analyse and prevent medication incidents. Until the program is fully operational, medication incidents and near misses (defined by ISMP Canada at www.ismp-canada.org/definitions.htm) should be reported to ISMP Canada (www.ismp-canada.org; email info@ismp-canada.org; tel 866 544-7672). If you suspect an adverse reaction, please submit the case to Health Canada (www.healthcanada.gc.ca/medeffect; tel 866 234-2345; fax 866 678-6789).[6]

Lili Loorand-Stiver, BScPhm, Health Canada

Fig. 1: Chloral hydrate and potassium chloride bottles before (left) and after (right) labelling changes made by the manufacturer.

References

1. Tsutaoka BT. Sedative-hypnotic agents. In: Olson KR, editor. *Poisoning & drug overdose*. 6th ed. New York: McGraw-Hill Companies, Inc.; 2004. p. 335.
2. Baselt RC. Chloral hydrate. In: Baselt RC. *Disposition of toxic drugs and chemicals in man*. 7th ed. Foster City: Biomedical Publications; 2004. p. 188.
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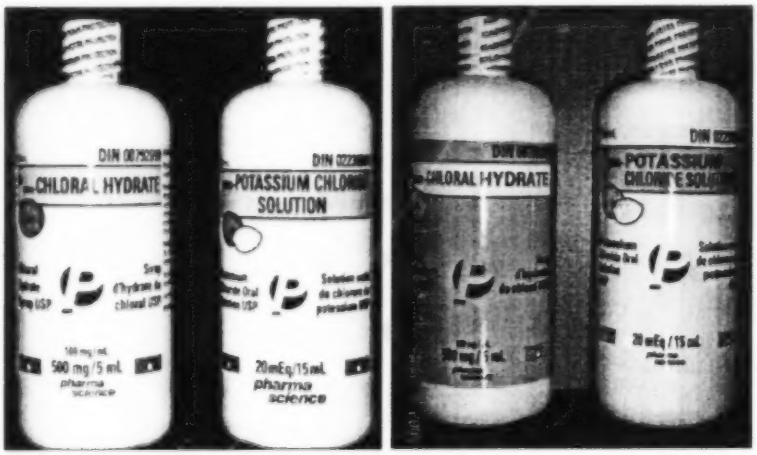

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Case presentation

Recent Canadian cases are selected based on their seriousness, frequency of occurrence or the fact that the reactions are unexpected. Case presentations are considered suspicions and are presented to stimulate reporting of similar suspected adverse reactions.

Ayurvedic medicines: lead contamination

A 53-year-old woman with rheumatoid arthritis was admitted to hospital because of fatigue, weakness, nausea and abdominal pain. Laboratory data showed anemia not associated with hemolysis or blood loss. Abnormal hematologic results were hemoglobin 77 (normally 115–155) g/L, hematocrit 0.24 (normally 0.35–0.45), red blood cell (RBC) count 2.8 (normally 3.8–5.1) $\times 10^{12}$/L and reticulocyte count 148 (normally 25–100) $\times 10^{9}$/L. Irregularly contracted RBCs and polychromasia were present. Packed RBCs and ferrous gluconate were administered; 6 days later the hematological parameters were improved, and the patient was discharged. Medications on admission were Pantoloc, Dicetel, Plaquenil and Eltroxin.

Two months after discharge, the patient admitted to having taken, for about 3 months, 2 Ayurvedic products purchased in India. Both products had been discontinued after the patient was in hospital. Laboratory analysis revealed that the 2 products contained lead, mercury and arsenic. At this time, the patient's blood lead level was 2.54 µmol/L. Three months after discharge, the patient's hematologic parameters were within normal ranges and her blood lead level had decreased.

Certain Ayurvedic products have been identified as being contaminated with heavy metals.[1-3]

References

1. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, Phillips RS. Heavy metal content of Ayurvedic herbal medicine products. *JAMA* 2004;292(23):2868-73.
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How to report adverse reactions

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Regional Adverse Reaction (AR) Centres

British Columbia
British Columbia Regional AR Centre
c/o BC Drug and Poison Information Centre
1081 Burrard St.
Vancouver BC V6Z 1Y6
adr@dpic.ca

Alberta
Alberta Regional AR Centre
c/o Ste. 730, 9700 Jasper Ave.
Edmonton AB T5J 4C3
Alberta_AR@hc-sc.gc.ca

Saskatchewan
Saskatchewan Regional AR Centre
c/o Saskatchewan Drug Information Service
College of Pharmacy and Nutrition
University of Saskatchewan
110 Science Place
Saskatoon SK S7N 5C9
Sask.AR@usask.ca

Manitoba
Manitoba Regional AR Centre
Rm. 114, 510 Lagimodière Blvd.
Winnipeg MB R2J 3Y1
Manitoba_AR@hc-sc.gc.ca

Ontario
Ontario Regional AR Centre
c/o LonDIS Drug Information Centre
London Health Sciences Centre
339 Windermere Rd.
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Québec
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c/o Drug Information Centre
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Atlantic
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For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
c/o Queen Elizabeth II Health Sciences Centre
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adr@cdha.nshealth.ca

All territories
National AR Centre
Marketed Health Products Safety and Effectiveness Information Division
Marketed Health Products Directorate
Tunney's Pasture, AL 0701C
Ottawa ON K1A 0K9
Tel: (613) 957-0337;
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Québec
Québec Regional AR Centre
c/o Drug Information Centre
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Atlantic
Atlantic Regional AR Centre
For New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador
c/o Queen Elizabeth II Health Sciences Centre
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All territories
National AR Centre
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Marketed Health Products Directorate
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Adverse reactions (ARs) to health products are considered to be suspicions, as a definite causal association often cannot be determined. Spontaneous reports of ARs cannot be used to estimate the incidence of ARs because ARs remain underreported and patient exposure is unknown.

Health Canada / Santé Canada

Canadian Adverse Drug Reaction Monitoring Program

Health Products and Food Branch
Direction générale des produits de santé et des aliments

• See page 4 for return address

Report of suspected adverse reaction due to **health products*** marketed in Canada

PROTECTED B**
(when completed)

• La version française de ce document est disponible à:
http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/form/ar-et_form_f.html

A. Patient Information
(See " Confidentiality " section below)

1. Identifier	3. Sex	4. Height	5. Weight
2. Age at time of reaction	☐ Male ☐ Female	_____ feet or _____ cm	_____ lbs or _____ kgs

B. Adverse Reaction

1. Outcome attributed to adverse reaction (check all that apply)

- ☐ Death_____ (dd/mm/yyyy)
- ☐ Life-threatening
- ☐ Hospitalization
- ☐ Hospitalization - prolonged
- ☐ Disability
- ☐ Congenital malformation
- ☐ Required intervention to prevent damage/permanent impairment
- ☐ Other : _____

2. Date of reaction			3. Date of this report		
DD	MM	YYYY	DD	MM	YYYY

4. Describe reaction or problem

5. Relevant tests / laboratory data (including dates (dd/mm/yyyy))

6. Other relevant history, including pre-existing medical conditions
(e.g. allergies, pregnancy, smoking and alcohol use, hepatic / renal dysfunction)

C. Suspected Health Product(s)
(See "How to report" section below)

1. Name (give labeled strength & manufacturer, if known)
1
2

2. Dose, frequency & route used	3. Therapy dates (if unknown, give duration)
# 1	# 1 From (dd/ mm/yyyy - To (dd/ mm/yyyy)
# 2	# 2

4. Indication for use of suspected health product	5. Reaction abated after use stopped or dose reduced
# 1	# 1 ☐Yes ☐No ☐Doesn't apply
# 2	# 2 ☐Yes ☐No ☐Doesn't apply

6. Lot # (if known)	7. Exp. date (if known)	8. Reaction reappeared after reintroduction
# 1	# 1 (dd /mm/yyyy)	# 1 ☐Yes ☐No ☐Doesn't apply
# 2	# 2	# 2 ☐Yes ☐No ☐Doesn't apply

9. Concomitant health products (name, dose, frequency and route used), and therapy dates (dd/mm/yyyy) (exclude treatment of reaction)

10. Treatment of adverse reaction (medications and / or other therapy), **include dates** (dd/mm/yyyy)

D. Reporter Information
(See " Confidentiality " section below)

1. Name, address & phone number

2. Health professional?	3. Occupation	4. Also reported to manufacturer?
☐Yes ☐No		☐Yes ☐No

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the adverse reaction.

*** Use this form to report suspected adverse reactions to pharmaceuticals, biologics (including fractionated blood products, as well as therapeutic and diagnostic vaccines), natural health products or radiopharmaceuticals.**

**** As per the Treasury Board of Canada Secretariat Government Security Policy.**

HC/SC 4016 (02/05)

Canada

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Summary of health professional and consumer advisories posted from May 19 to Aug. 18, 2005
(advisories are available at www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/index_e.html)

Date	Product	Subject and type
Aug 16	Albumin	Albumin therapy in critically ill patients: safety information — notice to hospitals
Aug 15	Lipitor	Counterfeit Lipitor sold in the United Kingdom: recall — consumer information
Aug 11	Anaesthetic vaporizers	Anaesthetic vaporizers: proper preventive maintenance — notice to hospitals
Aug 11	Sweet-Ease	Warning not to use Sweet-Ease pacifier dip — consumer information
Aug 9	Zometa and Aclasta	Zometa and Aclasta: renal safety — Novartis Pharmaceuticals Canada Inc. — consumer information and health professional communication
Aug 8 & May 30	Miracle II and Fortified Mineral Neutralizer	Warning not to use natural health products from Tedco Inc. and Master's Miracle — consumer information and consumer information update — consumer information
Aug 4 & July 18	Pacemakers	Safety information on certain pacemakers — consumer information — Guidant Canada Corporation, health professional communication
Aug 3	Opioids	Slow-release opioid painkillers and alcohol: interaction — consumer information
July 22, June 24, 20 & 17	Cardiac defibrillators	Implantable cardiac defibrillators: safety information — Guidant Canada Corporation — Update on Ventak Prizm AVT, Vitality AVT and Contak Renewal AVT, health professional communication — Contak Renewal 3 and 4, Renewal 3 and 4 AVT, and Renewal RF, health professional communication — Contak Renewal (Model H135) and Contak Renewal 2 (Model H155), health professional communication — Ventak Prizm AVT, Vitality AVT and Contak Renewal AVT, health professional communication — Ventak Prizm 2 DR, Model 1861, health professional communication
July 28 & 22	Paxil, Paxil CR and pimozide	Paxil, Paxil CR and pimozide (Orap): concomitant use — GlaxoSmithKline Inc. — consumer information and health professional communication
July 26	Viagra, Cialis and Levitra	Viagra, Cialis and Levitra: vision problems — consumer information
July 21	Colleague pumps	Recall of certain Colleague volumetric infusion pumps — Baxter Corporation — notice to hospitals
July 20	Vail enclosed beds	Vail enclosed beds: potential patient entrapment — notice to hospitals
July 14	Ayurvedic products	Warning not to use certain Ayurvedic medicinal products — consumer information
July 12	Statins	Statins: safety information — consumer information
June 30	Clozaril (clozapine)	Clozaril: white blood cell monitoring (reminder) — Novartis Pharmaceuticals Canada Inc. — consumer information
June 30	Depo-Provera	Depo-Provera: bone mineral density changes — Pfizer Canada Inc. — consumer information and health professional communication
June 22 & 15	Atypical antipsychotics	Atypical antipsychotic drugs in dementia: safety information — consumer information and health professional communication
June 9	Videx, Viread, Sustiva and Viramune	Videx, Viread, Sustiva and Viramune: co-administration — Bristol–Myers Squibb Canada and Gilead Sciences Inc. — health professional communication
June 9	Refludan	Refludan: dosage and administration — Berlex Canada Inc. — notice to hospitals
June 7	GHR-15	Warning not to use GHR-15 — consumer information
May 19	Tubersol	Tubersol: serious allergic reactions — Sanofi Pasteur Limited — health professional communication

To receive the Newsletter and health product Advisories free by email, join Health Canada's *MedEffect* mailing list. *Go to* **www.hc-sc.gc.ca/dhp-mps/medeff/subscribe-abonnement/index_e.html**

New MedEffect Web site

MedEffect is a new Health Canada Web site dedicated to adverse reaction (AR) information. It provides health professionals and consumers access to new health product safety information, guidelines and forms for reporting suspected ARs. A searchable AR database can also be accessed through MedEffect. You can visit MedEffect at: **www.healthcanada.gc.ca/medeffect**

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Suggestions?
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